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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,738	02/21/2007	Ola Winqvist	20084-002US1	9383

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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
03/11/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/530,738	WINQVIST ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8 and 10-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-8 and 10-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/21/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed December 21, 2009 in response to the Office Action of June 19, 2009 is acknowledged and has been entered. Previously pending claims 2-4 and 9 have been cancelled, claims 1, 8 and 10 have been amended and new claims 11-18 have been added. Claims 48, 49, and 55-61 are currently being examined.

Rejections Maintained

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1 and 5-8 and 11-17 remain or are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 90-109 of copending Application No.12/158,683 in view of Okamoto et al. (Cancer Immunol. and

Immunotherap. 1995 40-173-181) essentially for the reasons set forth in section 10 of the Office Action of June 19, 2009, which are set forth below.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept and would have been obvious in view of the of copending claims which have all of the characteristics of a method for treating and/or and preventing the recurrence of cancer, which comprises the steps of a) providing lymphocytes obtained from sentinel lymph nodes from a patient; b) and expanding the lymphocytes in vitro, exposing the lymphocytes to an autologous tumor extract and antigen presenting B-cells. The claims are not drawn to using cytokines or anti-CD3 and/or anti-CD28 antibody.

Okamoto et al. teach culturing lymphocytes from tumor draining lymph nodes of mice with melanomas in recombinant IL-2, anti-CD3 monoclonal and activated B cells to expand CD8+ T-cell lymphocytes, see p. Title, Abstract, and Materials and Methods, p. 173-174 and Fig. 1-3. Okamoto et al. teach treating tumors with the expanded lymphocytes, see Abstract, Tables 1 and 2, and Figures 5 and 6.

Thus, it would have been prima facie obvious to add IL-2 or anti-CD3 monoclonal antibody to the expansion of T-lymphocytes, because Okamoto teach that IL-2 or anti-CD3 monoclonal antibody stimulate CD8+ T-cell expansion, thus one of skill in the art would have been motivated with a reasonable expectation of success to use IL-2 or anti-CD3 monoclonal antibody because they were known and used in the art for this purpose.

This is a provisional obviousness-type double patenting rejection.

Applicants argue that the allegedly conflicting claims of application serial numbers 12/158,683, 12/158,680, and 12/147,752 have not been patented. For this reason, the present rejections are a provisional obviousness-type double patenting rejections. In view of the remarks presented herein, it is applicants' understanding that the provisional obviousness- type double patenting rejections are the only rejections remaining in the present application. Accordingly, the double patenting rejections should be withdrawn to permit the present application to issue as a patent. See MPEP § 804.I.B. Because none of application serial numbers 12/158,683, 12/158,680, and 12/147,752 has issued as a patent, no terminal disclaimer is required for the present application. Applicants respectfully request that the Examiner withdraw the rejection.

Applicants' arguments have been considered, but have not been found persuasive because the provisional obviousness- type double patenting rejections are not the only rejections remaining in the present application. Additionally, sentinel lymph nodes from a human cancer patient are within the scope of the claims of application number 12/158,683. See Example 1 of 12/158,683.

3. Claims 1 and 5-8 and 11-17 remain or are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 90-109 of copending Application No.12/158,680 in view of Okamoto et al. (Cancer Immunol. and Immunotherap. 1995 40-173-181) essentially for the reasons set forth in section 11 of the Office Action of June 19, 2009, which are set forth below.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept and would have been obvious in view of the of copending claims which have all of the characteristics of a method for treating and/or and preventing the recurrence of cancer, which comprises the steps of a) providing lymphocytes obtained from sentinel lymph nodes from a patient; b) and expanding the lymphocytes in vitro, exposing the lymphocytes to an autologous tumor extract and antigen presenting B-cells. The claims are not drawn to using cytokines or anti-CD3 and/or anti-CD28 antibody.

Okamoto et al. teach culturing lymphocytes from tumor draining lymph nodes of mice with melanomas in recombinant IL-2, anti-CD3 monoclonal and activated B cells to expand CD8+ T-cell lymphocytes, see p. Title, Abstract, and Materials and Methods, p. 173-174 and Fig. 1-3. Okamoto et al. teach treating tumors with the expanded lymphocytes, see Abstract, Tables 1 and 2, and Figures 5 and 6.

Thus, it would have been prima facie obvious to add IL-2 or anti-CD3 monoclonal antibody to the expansion of T-lymphocytes, because Okamoto teach that IL-2 or anti-CD3 monoclonal antibody stimulate CD8+ T-cell expansion, thus one of skill in the art would have been motivated with a reasonable expectation of success to use IL-2 or anti-CD3 monoclonal antibody because they were known and used in the art for this purpose.

This is a provisional obviousness-type double patenting rejection.

Applicants argue that the allegedly conflicting claims of application serial numbers 12/158,683, 12/158,680, and 12/147,752 have not been patented. For this reason, the present

rejections are a provisional obviousness-type double patenting rejections. In view of the remarks presented herein, it is applicants' understanding that the provisional obviousness- type double patenting rejections are the only rejections remaining in the present application. Accordingly, the double patenting rejections should be withdrawn to permit the present application to issue as a patent. See MPEP § 804.I.B. Because none of application serial numbers 12/158,683, 12/158,680, and 12/147,752 has issued as a patent, no terminal disclaimer is required for the present application. Applicants respectfully request that the Examiner withdraw the rejection.

Applicants' arguments have been considered, but have not been found persuasive because the provisional obviousness- type double patenting rejections are not the only rejections remaining in the present application. Additionally, sentinel lymph nodes from a human cancer patient are within the scope of the claims of application number 12/158,680. See Example 1 of 12/158,680.

4. Claims 1 and 5-8 and 11-17 remain or are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 1-33 of copending Application No.12/147,752 in view of Okamoto et al. (Cancer Immunol. and Immunotherap. 1995 40-173-181) essentially for the reasons set forth in section 12 of the Office Action of June 19, 2009, which are set forth below. .

Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept and would have been obvious in view of the of copending claims which have all of the characteristics of a method for treating and/or and preventing the recurrence of cancer, which comprises the steps of a) providing lymphocytes obtained from sentinel lymph nodes from a patient; b) and expanding the lymphocytes in vitro, exposing the lymphocytes to an autologous tumor extract and antigen presenting B-cells. The claims are not drawn to using cytokines or anti-CD3 and/or anti-CD28 antibody.

Okamoto et al. teach culturing lymphocytes from tumor draining lymph nodes of mice with melanomas in recombinant IL-2, anti-CD3 monoclonal and activated B cells to expand

CD8+ T-cell lymphocytes, see p. Title, Abstract, and Materials and Methods, p. 173-174 and Fig. 1-3. Okamoto et al. teach treating tumors with the expanded lymphocytes, see Abstract, Tables 1 and 2, and Figures 5 and 6.

Thus, it would have been prima facie obvious to add IL-2 or anti-CD3 monoclonal antibody to the expansion of T-lymphocytes, because Okamoto teach that IL-2 or anti-CD3 monoclonal antibody stimulate CD8+ T-cell expansion, thus one of skill in the art would have been motivated with a reasonable expectation of success to use IL-2 or anti-CD3 monoclonal antibody because they were known and used in the art for this purpose.

This is a provisional obviousness-type double patenting rejection.

Applicants argue that the allegedly conflicting claims of application serial numbers 12/158,683, 12/158,680, and 12/147,752 have not been patented. For this reason, the present rejections are a provisional obviousness-type double patenting rejections. In view of the remarks presented herein, it is applicants' understanding that the provisional obviousness- type double patenting rejections are the only rejections remaining in the present application. Accordingly, the double patenting rejections should be withdrawn to permit the present application to issue as a patent. See MPEP § 804.I.B. Because none of application serial numbers 12/158,683, 12/158,680, and 12/147,752 has issued as a patent, no terminal disclaimer is required for the present application. Applicants respectfully request that the Examiner withdraw the rejection.

Applicants' arguments have been considered, but have not been found persuasive because the provisional obviousness- type double patenting rejections are not the only rejections remaining in the present application. Additionally, sentinel lymph nodes from a human cancer patient are within the scope of the claims of application number 12/147,752. See Example 1 and 2 of 12/147,752.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 10 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 contains the trademark/trade name lymphazurin blue. See Wedgewood Pharmacy (http://www.wedgewoodpharmacy.com/isosulfan/ 2004)). Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe patent blue dye and, accordingly, the identification/description is indefinite. Additionally given that patent blue dye and lymphazurine blue appear to be the same substance, see ee Wedgewood Pharmacy, the intended difference in scope of the two compounds cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 5-8, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating cancer, which comprises the steps of: a) providing lymphocytes obtained from sentinel lymph nodes from a human cancer patient;

b) expanding the lymphocytes in vitro, wherein the lymphocytes are stimulated in vitro by the addition of a substance selected from the group consisting of IL-2, IL-12, an anti-CD3 antibody, and an anti-CD28 antibody; and c) transferring the expanded lymphocytes back into the patient OR a kit comprising (I) a dye selected from the group consisting of patent blue dye, lymphazurine blue, and 99Tc labeled albumin and (ii) a substance selected from the group consisting of IL-2, IFN-a, IL-12, an anti-IL-4 antibody, an anti-CD3 antibody, and an anti-CD28 antibody, *does not* reasonably provide enablement for a method for treating cancer , which comprises the steps of: a) providing lymphocytes obtained from sentinel lymph nodes from a human cancer patient; b) expanding the lymphocytes in vitro, wherein the lymphocytes are stimulated in vitro by the addition of a substance selected from the group consisting of IL-2, *IFN-a, an anti-IL-4* antibody, an anti-CD3 antibody, and an anti-CD28 antibody; and c) transferring the expanded lymphocytes back into the patient OR a kit comprising (i) a dye selected from the group consisting of patent blue dye, lymphazurine blue, and 99Tc labeled albumin and (ii) a substance *capable to stimulate proliferation of lymphocytes* selected from the group consisting of IL-2, IFN-a, IL-12, an anti-IL-4 antibody, an anti-CD3 antibody, and an anti-CD28 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations."

(Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1, 5-8, and 11 are drawn to a method for treating cancer , which comprises the steps of: a) providing lymphocytes obtained from sentinel lymph nodes from a human cancer patient; b) expanding the lymphocytes in vitro, wherein the lymphocytes are stimulated in vitro by the addition of a substance selected from the group consisting of IL-2, IFN-a, IL-12, an anti-IL-4 antibody, an anti-CD3 antibody, and an anti-CD28 antibody; and c) transferring the expanded lymphocytes back into the patient. Claim 10 is drawn to a kit comprising (i) a dye selected from the group consisting of patent blue dye, lymphazurine blue, and 99Tc labeled albumin and (ii) a substance *capable to stimulate proliferation of lymphocytes* selected from the group consisting of IL-2, IFN-a, IL-12, an anti-IL-4 antibody, an anti-CD3 antibody, and an anti-CD28 antibody.

The specification teaches that the lymphocytes from sentinel lymph nodes are exposed to stimulating agents for expansion, such as with CD3, phorbol ester with a calcium ionophore, or with an anti-CD3 antibody and an anti-CD28 antibody to stimulate proliferation of T cells, see p. 6- lines 15-24. The specification teaches that T-cells obtained from lymph nodes may be stimulated for maintenance and expansion with IL-2, see p. 7-lines 13 and 14. The specification teaches that IL-12, INF-alpha and anti-IL4 antibody can be used to activated CD4+ T helper cells toward IFN-gamma producing Th1 effector cells, see p. 7-lines 13 and 14. Thus, the stimulation

of lymphocytes encompasses inducing cell proliferation of lymphocytes. The specification teaches the stimulation and induction of proliferation of T-cells from sentinel lymph nodes with Concanavalin A and IL-2, see Example 2 and p. 12.

One of skill in the art cannot extrapolate the teachings of the specification to enable the scope of the claims because the stimulation or activation, including inducing cell growth, of lymphocytes with cytokines, antibodies, or other factors is cell type, context and factor dependent and one of skill in the art would not predictably be able to stimulate the growth of all lymphocytes from sentinel lymph nodes of a patient with the claimed cytokines or antibodies. In particular, Janeway et al. (Immunobiology 5, Garland Science, 2001, Figure A.24. previously cited) teach that lymphocytes are made up of different subsets of B cells, T-cells, and natural killer cells. Additionally, Janeway et al. (Immunobiology 5, Garland Science, 2001, Appendix III, previously cited) teach that there are various cytokines that stimulate proliferation of different types of lymphocytes, but does not teach any substance that can stimulate all lymphocytes. Furthermore, with regard to the specifically claimed cytokines and antibodies for stimulation of lymphocytes, Harada et al. (Immunology 1996 87: 447-453, previously cited) teaches that CD28 antibody does not work alone to stimulate the expansion of lymphocytes see Table 2. Additionally, US Pat. App. Pub. 2002/0182730 (Gruenberg et al. July 31, 1998, previously cited) teaches that antibodies to IL-4 promote the differentiation of T cells, not proliferation, see para 0091-0094, and USPN 5,767,065 (Mosley et al. 1998, previously cited) teaches that anti-IL4 antibody inhibits Il-4 induced B-cell proliferation, see Fig. 7. Furthermore, Spits et al. (J. Immunology 1987 139: 1142-1147, previously cited) teach that IL-4 stimulates B-cell and T-cell growth factor activities. See abstract. However, Hofman et al. (J. Immunology

1988 141:1185-1190, previously cited) teach that IL-4 can induce differentiation of pre-B cells in the presence of IL-3 and the supernatant from a T-cell line, see Abstract and p.1188. Thus, the effects of cytokines like IL-4 and antibodies to them are context and cell type specific. Furthermore, Biron (Immunity 2001 14: 661-664, previously cited) teach that the lymphocyte responses to IFN alpha are dependent upon the context in which it is present, see Figure 1. Given that the response of lymphocytes to stimuli like cytokines and antibodies is cell type, context and factor dependent and in the absence of sufficient guidance or exemplification from the specification that IFN-a and an anti-IL-4 antibody can be used to expand lymphocytes or that lymphocytes stimulated with these cytokines can be used to treat cancer one of skill in the art would not be predictably be able to use the method as claimed without undue experimentation.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Applicants argue that independent claim 1 has been amended to delete the reference to "preventing" cancer and to include a step of "transferring the expanded lymphocytes back into the patient." It is applicants' understanding that these amendments overcome, at least in part, the present rejection.

Applicants argue that the currently claimed invention is based, at least in part, on the inventors' surprising discovery that sentinel lymph nodes isolated from cancer patients harbor

lymphocytes showing activity against tumor cells. In contrast to the sentinel lymph node-derived cells, lymphocytes isolated from peripheral blood or generically from the lymph system of the patients were unresponsive towards the tumor. Consistent with this discovery, the method of independent claim 1 includes steps of expanding in vitro lymphocytes obtained from sentinel lymph nodes from a human cancer patient and transferring the expanded lymphocytes back into the patient. Furthermore, the in vitro expansion step entails stimulation of the lymphocytes with IL-2, IFN-a, IL-12, an anti-IL-4 antibody, an anti-CD3 antibody, or an anti-CD28 antibody. The skilled artisan having read the present specification would have readily understand that any of these means of stimulating lymphocytes would be effective means to induce expansion of the sentinel lymph node-derived lymphocytes.

Applicants argue that in view of the foregoing comments, applicants respectfully submit that the person of ordinary skill in the art, at the time the present application was filed, would have been able to practice the claimed methods without undue experimentation and with a reasonable expectation of success. As a result, applicants request that the Examiner withdraw the rejection.

Applicants arguments have been considered, but have not been found persuasive because neither the specification nor the art of record has shown that stimulation of lymphocytes with IFN-a or an anti-IL-4 antibody will expand lymphocytes in vitro or that lymphocytes so treated will be useful for treating cancer. Thus, given these substances have growth inhibitory properties to lymphocytes, such as antibodies to IL-4 being growth inhibitory, and the response of lymphocytes to IL4 antibody and IFN-a may be context dependent, one of skill in the art

could not predictably use an anti-IL4 antibody and IFN-1 in the claimed method or for stimulating proliferation of lymphocytes without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 5-8 and 11-17 are anticipated by Meijer et al. (J. Clin. Pharmacol. July 2001 441:81S-94S).

Meijer et al. teach using sentinel, tumor draining lymph nodes from human cancer patients in clinical trials for adoptive immunotherapy. Meijer et al. teach that the patients were inoculated with autologous tumor cells, the tumor draining lymph nodes lymphocytes were harvested, expanded with IL-2 and/ or anti-CD3 antibody and returned to the patient. See p. 85S and 86S and Fig. 2. It is noted that the exposure of the lymphocytes to an additional activation signal, given the comprising language, is not limited to occurring *in vitro*. Meijer et al. teaches that the injected tumor vaccine cells are processed by dendritic cells that migrate to the draining lymph node where the dendritic cells present the lymphocytes with the tumor cell extracted peptides. See p. 83S-84S and Fig. 1. Thus, the lymphocytes are activated by antigen presenting dendritic cells with autologous tumor extracts. Additionally, it is noted that a recombinant antigen is a product made by a process, i.e. an antigen made recombinantly and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim.

See *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the autologous tumor extract peptides anticipate the recombinant antigen of claim 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 5-8 and 11-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chin and Bear (Annals of Surgical Oncology 2002 Jan-Feb; 9(1):94-103, IDS), in view of Okamoto et al. (Cancer Immunol. and Immunotherap. 1995 40-173-181, previously cited), in further view of Santin et al. (Am J. Obstetric. Gynceol. Sep. 2000, 183: 601-609) and in further view of Kan et al. (Biotherapy, 6:245-250 1994).

Chin and Bear teach culturing lymphocytes from the sentinel lymph nodes from a mouse with a mammary tumor and expanding the lymphocytes in a culture with recombinant cytokine IL-2 and ionomycin to activate expansion of the cells, see p. 95- Materials and Methods and Fig. 2. Chin and Bear teach treating tumors with said expanded lymphocytes, see Abstract and Fig. 1 and 3. Chin and Bear teach that clinical application the sentinel node technique to identify the more potent lymphocytes from the tumor draining lymph nodes may allow a more focused and precise lymphadenectomy procedure. Chin and Bear teach that the draining lymph nodes have the most potent anti-tumor activity. See p. 103-1st col.

Chin and Bear do not teach sentinel lymph nodes from a human cancer patient or using autologous tumor extract or antigen presenting cells to stimulate the lymphocytes

Okamoto et al. teach culturing lymphocytes from tumor draining lymph nodes of mice with melanomas in recombinant IL-2, anti-CD3 monoclonal and activated B cells to expand the lymphocytes, see p. Title, Abstract, and Materials and Methods, p. 173-174 and Fig. 1-3. Okamoto et al. teach treating tumors with the expanded lymphocytes, see Abstract, Tables 1 and 2, and Figures 5 and 6. Okamoto et al. teach that co-stimulatory molecules are essential for the effective induction of effector T cells for tumor eradication in vivo. See p. 180-2nd col.

Okamoto et al. teach that the culture system is clinically simple and are planning to apply the system to clinical trials. See p. 180-2nd col.

Santin et al. teach that dendritic cells pulsed with autologous human ovarian cells stimulate cytotoxic T cell to consistently kill autologous tumor cells. See Abstract and Fig. 1. Santin et al. teach that dendritic cells for are the most effective antigen presenting cells for naïve T-cell activation. See p. 602- 1st col.

Kan et al. teach stimulating human patient lymphocytes with autologous tumor extract in culture and using the so stimulated autologous lymphocytes for immunotherapy. See Abstract and p. 246. Kan et al. teach that they have achieved a response rate of 64-65% using this method. See p. 245- Introduction.

It would have been *prima facie* obvious at the time the invention was made in view of the combined teachings of Chin and Bear, Okamoto et al., Santin et al. and Kan et al. to use human sentinel lymph nodes from a human cancer patient stimulated with autologous tumor extracts, dendritic cells loaded with tumor cell extract or B-cells because the Chin and Bear teach that sentinel, tumor draining lymph nodes have the most potent tumor activity, Okamoto et al. teach that co-stimulation of T lymphocytes is important for anti-tumor activity of lymphcytes, and Okamoto et al. Santin et al. and Kan et al. teach effective methods of stimulating the anti-tumor cell activity of lymphocytes with autologous tumor extracts, dendritic cells, and B-cells. Given that Kan et al. observed clinical success with his adoptive immunotherapy in human patients, the more potent anti-tumor activity sentinel, tumor draining lymph nodes, and Chin and Bear and Okamoto et al. contemplated clinical use of the methods one of skill in the art would have been motivated with a reasonable expectation of success to combine the teachings of the art to identify

the most effective immunotherapeutic methods in humans using humans sentinel lymph nodes. Additionally, it is noted that a recombinant antigen is a product made by a process, i.e. an antigen made recombinantly and the patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claim. See *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Thus, the autologous tumor extract peptides anticipate the recombinant antigen of claim 11.

9. Claim 10 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2001/005433 (Goines et al. Jan. 2001), in view of Chin and Bear (Annals of Surgical Oncology 2002 Jan-Feb; 9(1):94-103, IDS) and in further view of Stratagene Catalog (1988, p. 39).

WO 2001/005433 teaches kits with patent blue dye and 99Tc labeled albumin. See claims 20-28, Examples 1, 5, 6, 8, and 9. WO 2001/005433 teaches marking sentinel lymph nodes with patent blue dye. See Example 15.

WO 2001/005433 does not teach IL-2, IFN-a, IL12, anti-IL-4 antibody, anti-CD3 antibody, or andti-CD28 antibody.

Chin and Bear (Annals of Surgical Oncology 2002 Jan-Feb; 9(1):94-103, IDS) teach using isosulfan blue (IB) (which is Patent Blue/Lymphazurine blue, See Wedgewood Pharmacy (http://www.wedgewoodpharmacy.com/isosulfan/ 2004)) to mark sentinel lymph nodes. See p. 95. Chin and Bear teach using IL-2 to expand the isolated lymphocytes for treatment. See p. 95-right col.

Stratagene Catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the IL-2 and patent blue dye of Chin and Bear into kits with patent blue or 99Tc labeled albumin as taught by WO 2001/005433 because these substances are necessary for the isolation and expansion of lymphocytes as taught by Chin and Bear that were used for therapy and having them in a kit format would make for their convenient use, storage, and distribution. In particular, Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1). Thus, one of skill in the art would have been motivated with a reasonable expectation of success to make a kit of IL-2 and patent blue or 99Tc labeled albumin given that substances are used in the same protocol of isolation and expansion of lymphocytes from sentinel lymph nodes taught in the art and to reduce waste, save money and resources, and provide quality control.

10. All other objections and rejections recited in Office Action of June 19, 2009 are withdrawn.

11. No claims allowed.

12. Applicant's amendment necessitated the new grounds of rejection. Thus **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Primary Examiner, Art Unit 1642